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Original Article

Outcome of patients with bulky IB (≥ 6 cm) cervical squamous cell carcinoma with and without cisplatin-based neoadjuvant chemotherapy

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ABSTRACT

Objective: To study the surgical morbidity and outcomes of patients with markedly bulky cervical squamous cell carcinoma (≥ 6 cm Cx-SCC) who underwent radical hysterectomy (RH) with and without neoadjuvant chemotherapy (NACT).
Materials and methods: This retrospective study enrolled patients with International Federation of Gynecology and Obstetrics (FIGO) IB markedly bulky Cx-SCC who were treated with either three courses of weekly single agent cisplatin NACT (50 mg/m2) and subsequent radical hysterectomy (NACT-RH) or direct radical hysterectomy (RH) between 1996 and 2001. A total of 60 patients fulfilled the criteria, including 35 and 25 patients with NsACT-RH and RH, respectively.
Results: There was no statistically significant difference in basic characteristics between the two groups, except the smaller pathological tumor size, less blood loss, and lower immediate complication rate in the NACT-RH group. Median survival was 143.8 months in the NACT-RH group and 129.8 months in the RH group, respectively, without a statistically significant difference. Multivariate analysis showed that large pathological tumor size [hazard ratio (HR) 10.66, 95% confidence interval (CI) 2.93–38.80], the presence of para-aortic lymph node metastases and an immediate complication (HR 8.33 and 4.55, 95% CI 1.66–41.75 and 1.35–15.27, respectively) contributed to a worse outcome.
Conclusion: Weekly single agent cisplatin NACT indeed reduced the pathological tumor size and immediate complication rate during the RH, supporting the feasibility of subsequent RH in the management of patients with bulky Cx-SCC.

Introduction

Cervical (Cx) cancer is still a serious health problem, second only to breast cancer as the most common female malignancy in both incidence and mortality worldwide [1]. In recent years, both overall survival (OS) and disease-free survival rates have been significantly improved as a result of advances in the technologies of surgery, chemotherapy (CT), and radiotherapy (RT) [2]. However, patients

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with early-stage bulky Cx cancer are difficult to manage, because of the high recurrence rate and worse prognosis, compared to those with smaller tumors at the same stage [3]. In this situation, the role of surgery [radical hysterectomy and pelvic lymph node dissection (RH and PLND)] is controversial [2], compared with the role of concurrent chemoradiotherapy (CCRT). CCRT is now considered the treatment of choice for patients who are not candidates for initial surgical therapy [4–7]. In clinical practice, Cx cancer is classified according to the clinical International Federation of Gynecology and Obstetrics (FIGO) staging system [1], and this is mainly based on clinical examination, which makes the selection of those that will benefit from surgical intervention much more difficult. Therefore, modification of the treatment strategy, including the use of neoadjuvant chemotherapy (NACT), RT (external beam RT or brachytherapy) and CCRT, is much more frequent either before or after surgery.

To perform successful surgery, the induction of tumor shrinkage might be of most importance. This not only facilitates radical excision but also makes reconstruction easier. Although many strategies can be used to bring about tumor shrinkage, chemotherapy may be effective. NACT is well accepted in the management of various types of tumor, such as breast cancer [8]. However, the application of NACT for Cx cancer is debated, although it is often used in Asia, Italy, and South America [2]. The theoretical rationale for the use of NACT in Cx cancer includes the aforementioned induction of tumor shrinkage to facilitate radical excision, and a possible sterilization of lymph nodes and parametrial tissues, thereby reducing the risk factors of adjuvant therapy after surgery [1]. NACT regimens for Cx cancer vary, ranging from single-agent to many forms of multiagent regimens. In addition, the therapeutic interval also varies, ranging from every week to every 2, 3, or 4 weeks [9–15]. The clinical effects of NACT are not always consistent with the theoretical benefits, and that is why there is a great deal of conflicting data in the literature [9–15]. The available reports on the effect of NACT on Cx cancer are mainly with regard to FIGO IB and IIA bulky tumors, sometimes up to stage IVA [9–16]. The heterogeneity of the study population, including the differences in stage and cell types, and comorbidity with other medical or surgical illnesses make it difficult to reach a conclusion [9–16]. In addition, there is no study addressing markedly bulky Cx squamous cell carcinoma (Cx-SCC) ($\geq$ 6 cm). Therefore, we conducted this retrospective study to investigate the effect of NACT on the management of early-stage bulky Cx-SCC before surgery.

Materials and methods

The population of this study was derived from the Cancer Registry in the Department of Obstetrics and Gynecology of Taipei Veterans General Hospital. All patients with markedly bulky $\geq$ 6 cm Cx-SCC undergoing RH and PLND between 1996 and 2001 were evaluated. The study aimed to compare the difference between weekly cisplatin-based NACT-RH and RH as an initial therapy for patients with $\geq$ 6 cm Cx-SCC. To make this study even more uniform and consistent, eligibility criteria were as follows: histologically verified uterine Cx-SCC; locally advanced stage FIGO IB disease without parametrial invasion or distant metastases; initial magnetic resonance image- or computed tomography-measurable tumor diameter $\geqq$ 6 cm in size; age younger than 65 years with a life expectancy $\geq$ 1 year; World Health Organization performance status of 0-2, treatment with type III RH and pelvic and para-aortic lymphadenectomy, no prior treatment with RT or CT, but three courses of weekly cisplatin 50 mg/m^2 were permitted; absence of prior malignant diseases or surgical illness, but cesarean section was permitted; and adequate renal, pulmonary, hepatic, bone marrow, and cardiac function.

Basic characteristics of the patients, including surgical parameters and complications, were recorded. Immediate complication included visceral organ injury, prolonged hospitalization because of instability or significant delay ($\geq$ 7 days) of immediate postoperative adjuvant therapy (such as CT, RT, or CCRT); difficulty in urination and constipation were excluded. Late complication included any therapy-related sequelae, such as long-term ureter or urethra catheter use ($\geq$ 12 months), radiation colitis, and cystitis. We used the following parameters to define the radiation colitis or radiation cystitis. The diagnosis of radiation colitis and/or cystitis was made when those patients who had at least one attack of anal bleeding and gross hematuria that required medical care for relief and the diagnosis of radiation colitis and/or cystitis had excluded other radiation-unrelated or tumor-related possibility at first, such as infection, acute gastroenteritis, hemorrhoid, or tumor recurrence.

Periodic follow-ups of patients, including postoperative adjuvant therapy, such as CT, RT, or CCRT in accordance with the patients' risk analysis [17–22], physical examination, vaginal cytology, and imaging or intravesical ureterography, continued until the patients died or for more than 5 years after surgery. To determine an appropriate decision point for the continuous data, such as age, tumor size, blood loss, and number of lymph nodes, the receiver operating characteristic was used [23].

Survival was determined on the basis of treatment and patient outcomes. Estimates of the proportion of OS were calculated by the Kaplan-Meier procedure, and differences in survival were evaluated via the log-rank test. Covariance analysis and the hierarchic Chi-square test were used to control for potential confounding factors in the comparison of clinicopathologic characteristics and risk factors. The log-rank test, hazard ratio (HR), and 95% confidence interval (CI) of mortality from cancer were calculated via the Cox proportional hazards model with univariate and multivariate analysis of OS. Statistical significance was determined by an unpaired two-tailed Student t test using a pooled estimator of variance, and was defined as $p < 0.05$. SPSS version 20 (SPSS, Chicago, IL, USA) was used for statistical analysis.

Results

A total of 60 patients fulfilled the aforementioned criteria and were enrolled into the analysis. Thirty-five patients received three cycles of weekly intravenous cisplatin 50 mg/m^2-based NACT, followed by RH and PLND and para-aortic lymph node sampling (NACT-RH group) on Day 18 after the first course of NACT. The remaining patients ($n = 25$) underwent RH and PLND and para-aortic lymph node sampling (RH group). Follow-up ranged from 11 months to 205 months (median 138 months).

There was no statistically significant difference in age, initial image tumor size, number of removed lymph nodes, cell grade, and presence of deep stromal invasion, vaginal invasion, parametrial invasion, lymphovascular invasion, and pelvic or para-aortic lymph node invasion between the two groups (Table 1). The percentage of patients in both groups who were treated with postoperative adjuvant therapy was also similar. The mortality rate seemed to be lower in the NACT-RH group (37.1% in the NACT-RH group and 48.0% in the RH group), although without a statistically significant difference. Pathological tumor size, estimated blood loss during operation, and immediate postoperative complications were significantly different between the two groups. In the NACT-RH group, the pathological tumor size was significantly smaller (4.5 $\pm$ 1.4 cm vs. 5.7 $\pm$ 0.8 cm, $p < 0.001$). In addition, a lesser amount of estimated blood loss during the RH procedure was also noted in the NACT-RH group (558 $\pm$ 1328 mL vs. 930 $\pm$ 356 ml, $p < 0.001$). The immediate postoperative complication rate overall

Table 1
Clinical characteristics of patients with bulky-sized squamous cell carcinoma of the cervix.

Characteristics	NACT + RH $n = 35$ (%)	RH $n = 25$ (%)	p
Age (y)	48.9 ± 9.3	50.5 ± 7.6	0.476
Image size (cm)	6.4 ± 0.5	6.2 ± 0.5	0.234
Pathological size (cm)	4.5 ± 1.4	5.7 ± 0.8	<0.001
Estimated blood loss (mL)	558 ± 1328	930 ± 356	<0.001
Number of pelvic LN metastasis	1.6 ± 2.6	1.4 ± 2.8	0.791
Number of removed pelvic LN	23.5 ± 5.0	26.3 ± 6.6	0.072
Number of para–aortic LN metastases	0.4 ± 1.0	0.24 ± 0.7	0.500
Number of removed para–aortic LN	2.6 ± 1.7	3.3 ± 2.1	0.158
Cell grade			
Good-to-moderate differentiation	30 (85.7%)	21 (84.0%)	0.944
Poor differentiation	5 (14.3%)	4 (16.0%)	
DSI (yes)	31 (88.6%)	23 (92.0%)	0.663
LVSI (yes)	22 (62.9%)	16 (64.0%)	0.928
Vaginal invasion (yes)	5 (14.3%)	3 (12.0%)	0.797
Parametrial invasion (yes)	3 (8.6%)	2 (8.0%)	0.937
Pelvic LN metastasis (yes)	13 (37.1%)	8 (32.0%)	0.681
Para–aortic LN metastasis (yes)	5 (14.3%)	3 (12.0%)	0.797
Adjuvant therapy (yes)	19 (54.3%)	16 (64%)	0.452
Types of adjuvant therapy			
None	16 (45.7%)	9 (36.0%)	0.669
CCRT	6 (17.1%)	7 (28.0%)	
CT	4 (11.4%)	4 (16.0%)	
RT	9 (25.7%)	5 (20.0%)	
Immediate complication (yes)	2 (5.7%)	8 (32.0%)	0.007
Late complication (yes)	7 (20.0%)	8 (32.0%)	0.290
Radiation-induced colitis	2 (5.7%)	4 (16.0%)	0.190
Radiation-induced cystitis	4 (11.4%)	4 (16.0%)	0.608
>12-mo ureter or urethra catheter use	3 (8.6%)	6 (24.0%)	0.099
Recurrence of disease (yes)	13 (37.1%)	12 (48.0%)	0.400
Recurrence site			
None	22 (62.9%)	13 (52.0%)	0.846
Pelvis	1 (2.9%)	1 (4.0%)	
Distant site	8 (22.9%)	8 (32.0%)	
Both	4 (11.4%)	3 (12.0%)	
Disease–free survival (mo)	99.7 ± 69.7	90.0 ± 72.1	0.602
Overall survival (mo)	107.6 ± 60.4	104.0 ± 60.2	0.821
Died of disease (yes)	13 (37.1%)	12 (48.0%)	0.400

CCRT = concurrent chemoradiation; CT = chemotherapy; DSI = deep stromal invasion; LN = lymph node; LVSI = lymphovascular space invasion; NACT = neoadjuvant chemotherapy; RT = radiation.

was 20%, but was lower in the NACT-RH group (5.7% vs. 32%, $p = 0.007$). Almost three-fifths of patients were treated with postoperative adjuvant therapy, such as CCRT, RT, and CT.

During the follow-up, 25 patients had recurrence, and all died of Cx cancer-related diseases. The overall survival rate was 58.3%. In the NACT-RH group, the OS rate was 62.9%, compared with 52% in the RH group (Fig. 1). The median survival time of the patients in the NACT-RH and RH groups was 143 months (ranging from 23.4 to 205.7 months) and 129 months (ranging from 11.2 to 203.5 months), respectively. Although the OS rate of the NACT-RH group seemed to be longer, it did not reach a statistically significant level ($p = 0.512$). The Kaplan-Meier procedure identified the significant prognostic factors as (A) pathological tumor size (≤ 5.3 cm vs. > 5.3 cm, $p < 0.001$), (B and C) presence of pelvic or para-aortic lymph node metastases (no vs. yes, $p < 0.001$), (D and E) presence of immediate or late complication (no vs. yes, $p = 0.002$, and $p = 0.020$, respectively), and (F) recurrence (no vs. yes, $p = 0.004$) (Fig. 2). In addition, patients who had a long-term urinary difficulty had a worse outcome (HR 2.93, 95% CI 1.21–-7.08).

Because the decision of postoperative adjuvant therapy was made in accordance with the patients' risk analysis [17–22], and most decisions were based on histopathological findings, such as a large-sized tumor, positive invasion of the cut end, presence of pelvic and/or para-aortic lymph nodes, and deep stromal invasion (Table 2), all would contribute to the worse prognosis, although

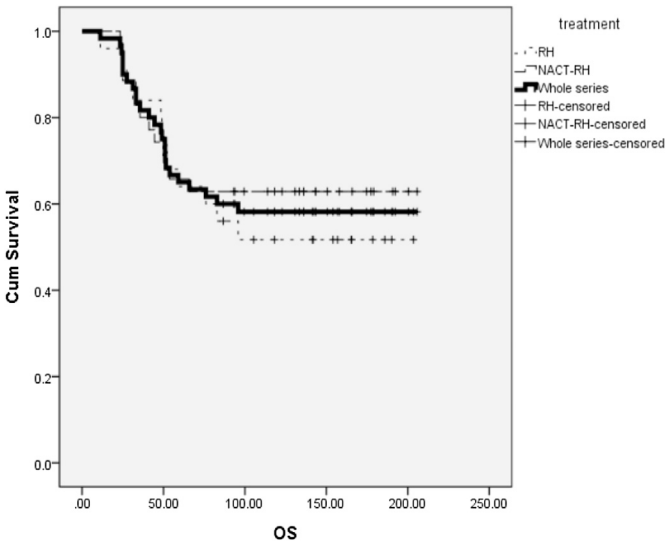

Fig. 1. Overall survival (OS) of all patients with bulky squamous cell carcinoma of the cervix (≥ 6 cm) undergoing primary treatment with either three courses of weekly cisplatin neoadjuvant therapy and radical hysterectomy (NACT-RH) or direct radical hysterectomy (RH). The OS rate of all patients was 58.3%, that of the NACT-RH group was 62.9%, and that of the RH group was 52%. $p = 0.512$.

many were not statistically significant in multivariate analysis (Table 3). Therefore, those patients who were treated with postoperative adjuvant therapy might have more badly pathological risk factors than those patients without adjuvant therapy. Table 2 confirmed this finding. Among these pathological risk factors, the presence of lymph node metastases either in the pelvis or para-aortic area was statistically significantly frequently found in patients who were treated with adjuvant therapy. These findings might explain why these patients after adjuvant therapy still had a worse outcome (Fig. 3).

Multivariate analysis showed that large pathological tumor size (HR 10.66, 95% CI 2.93–38.80), the presence of para-aortic lymph node metastases, and an immediate complication (HR 8.33 and 4.55, 95% CI 1.66–41.75 and 1.35–15.27, respectively) contributed to a worse outcome (Table 3).

Discussion

In our database, 60 of 689 patients (8.7%) undergoing RH within the study period received the diagnosis of Cx-SCC ≥ 6-cm. Compared to those with smaller tumors at the same stage, early-stage bulky Cx-SCC has long been recognized as high risk, because of the high recurrence rate and worse prognosis [3]. Many strategies have been used in an attempt to improve the prognosis and/or survival, especially for those patients who were treated mainly with surgery. The role of NACT in markedly bulky Cx-SCC was evaluated in this study. In agreement with the aforementioned reports, the OS rate of all patients, whether or not NACT was used, was 58.3%.

This rate was inferior to the OS of those patients with FIGO IB Cx-SCC or conventionally defined FIGO IB2 (a cut value of the tumor size ≥ 4-cm Cx-SCC) who were treated with RH and PLND as the primary treatment in our hospital, because the 5-year OS rate ranged from 78% to 92% during different study periods [17–19,22,24].

Compared with recent studies on NACT [7,9–16], the main difference in this study was the use of a single agent—cisplatin high-dose density CT (50 mg/m^2) —with a very short interval before surgery (18 days in our study), even though this dose seemed to be

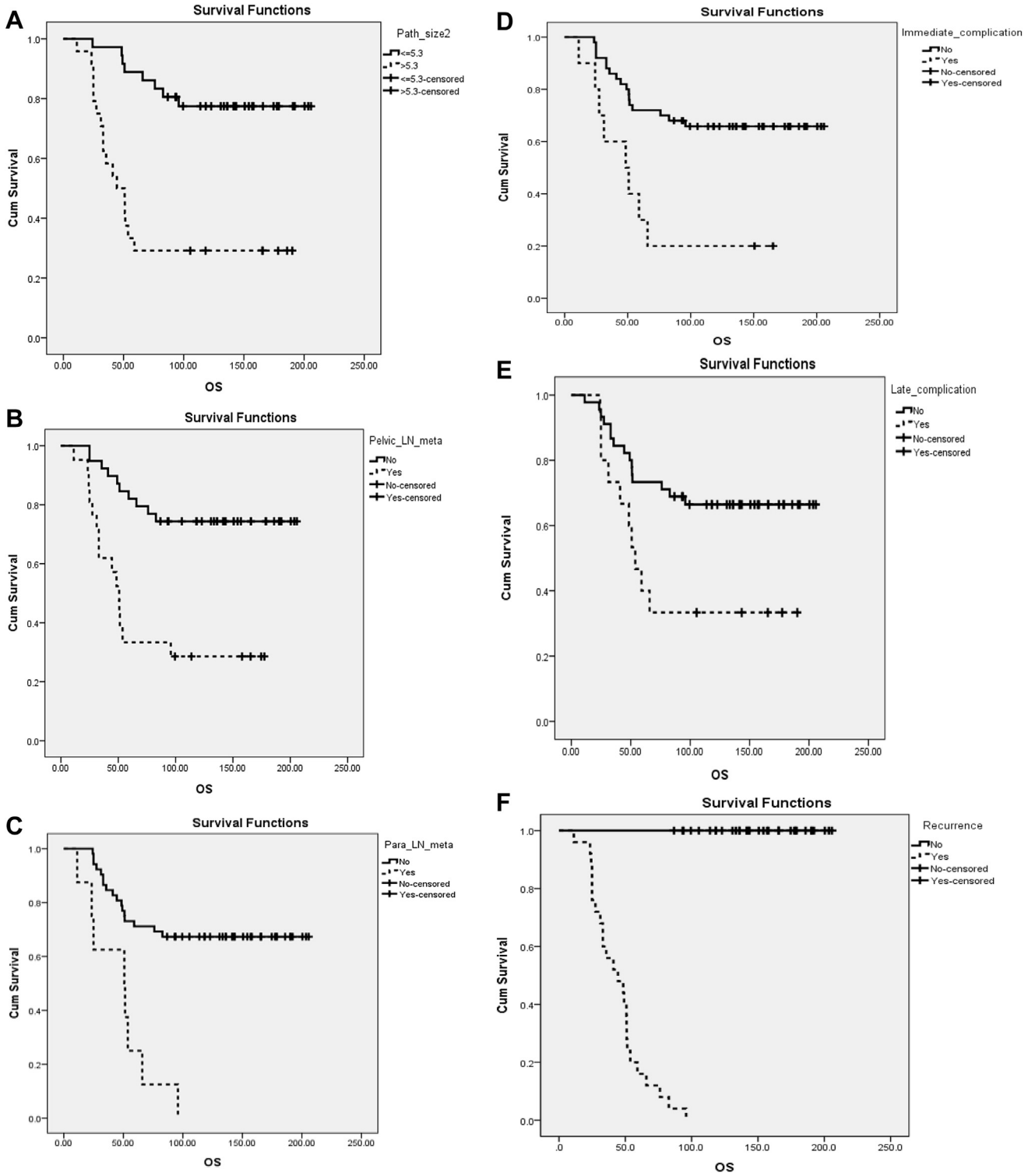

Fig. 2. The following parameters are prognostic factors of the patients with bulky squamous cell carcinoma of the cervix (≥ 6 cm) undergoing either three courses of weekly cisplatin neoadjuvant therapy and radical hysterectomy or direct radical hysterectomy: (A) pathological size (≤ 5.3 cm vs. >5.3 cm, $p < 0.001$); (B) presence or absence of pelvic lymph node metastases ($p < 0.001$); (C) presence or absence of para-aortic lymph node metastases ($p < 0.001$); (D) presence or absence of immediate complication ($p = 0.002$); (E) presence or absence of late complication ($p = 0.020$); and (F) occurrence of recurrence ($p = 0.004$). LN meta = lymph node metastasis; OS = overall survival.

significantly lower than the frequently used dosage of 75 mg/m^2 [15]. The concept that a shorter cycle length in combination with higher dose intensity tended to show an advantage for NACT was supported by a recent study [15]. Mountzios et al [25] suggested that the interval between CT should not exceed 14 days and the dose of cisplatin has to be greater than 25 mg/m^2 per week. This is important not only for surgery but also from a quality-of-life perspective (psychological aspect) [15]. As mentioned previously, in theory, NACT provides benefits not only during surgery but also postoperatively. NACT can reduce both tumor volume and lymph

Table 2
Clinical characteristics of patients with and without adjuvant therapy.

Characteristics	No adjuvant treatment, $n = 25$ (%)	Adjuvant therapy, $n = 35$ (%)	p
Image size (cm)	6.2 ± 0.4	6.5 ± 0.6	0.017
Pathological size (cm)	4.7 ± 1.3	5.2 ± 1.3	0.114
Cell grade			
Good-to-moderate differentiation	23 (92.0%)	28 (80.0%)	0.199
Poor differentiation	2 (8.0%)	7 (20.0%)	
DSI (yes)	24 (96.0%)	30 (85.7%)	0.190
LVSI (yes)	17 (68.0%)	21 (60.0%)	0.526
Vaginal invasion (yes)	2 (8.0%)	6 (17.1%)	0.304
Parametrial invasion (yes)	1 (4.0%)	4 (11.4%)	0.305
Pelvic LN metastasis (yes)	0 (0.0%)	21 (60.0%)	<0.001
Para-aortic LN metastasis (yes)	0 (0.0%)	8 (22.9%)	0.010

DSI = deep stromal invasion; LN = lymph node; LVSI = lymphovascular space invasion.

Table 3
Univariate and multivariate Cox regression analyses.

Characteristics	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p	HR (95% CI)	p
Treatment				
RH	1 (Ref)		1 (Ref)	
NACT + RH	0.77 (0.35–1.69)	0.514	0.83 (0.26–2.65)	0.753
Age (y)				
≤ 50	1 (Ref)		1 (Ref)	
> 50	1.05 (0.48–2.31)	0.900	1.89 (0.59–6.06)	0.282
Image size (cm)				
≤ 6	1 (Ref)		1 (Ref)	
> 6	1.67 (0.75–3.72)	0.212	1.83 (0.41–5.32)	0.546
Pathological size (cm)				
≤ 5.3	1 (Ref)		1 (Ref)	
> 5.3	5.45 (2.32–12.77)	< 0.001	10.66 (2.9–38.80)	< 0.001
Blood loss (mL)				
≤ 650	1 (Ref)		1 (Ref)	
> 650	1.62 (0.74–3.55)	0.231	1.61 (0.55–4.76)	0.385
Number of removed pelvic LN				
≤ 23	1 (Ref)			
> 23	0.58 (0.27–1.27)	0.175		
Number of removed para-aortic LN				
≤ 3	1 (Ref)			
> 3	1.35 (0.61–3.00)	0.466		
Cell grade				
1	1 (Ref)			
2	1.63 (0.22–12.11)	0.634		
3	1.18 (0.12–11.33)	0.887		
DSI				
No	1 (Ref)		1 (Ref)	
Yes	0.27 (0.10–0.73)	0.010	0.30 (0.07–1.37)	0.121
LVSI				
No	1 (Ref)		1 (Ref)	
Yes	1.44 (0.60–3.45)	0.414	1.07 (0.25–4.57)	0.925
Vaginal invasion				
No	1 (Ref)		1 (Ref)	
Yes	0.53 (0.13–2.26)	0.392	2.57 (0.34–19.77)	0.364
Parametrial invasion				
No	1 (Ref)		1 (Ref)	
Yes	0.39 (0.05–2.87)	0.354	0.86 (0.08–9.63)	0.903
Pelvic LN metastasis				
No	1 (Ref)		1 (Ref)	
Yes	4.41 (1.97–9.89)	< 0.001	2.76 (0.68–11.19)	0.156
Para-aortic LN meta				
No	1 (Ref)		1 (Ref)	
Yes	4.99 (2.12–11.74)	< 0.001	8.33 (1.66–41.75)	0.010
Adjuvant therapy				
No	1 (Ref)		1 (Ref)	
Yes	2.93 (1.17–7.35)	0.022	1.73 (0.28–10.87)	0.557
Types of adjuvant therapy				
None	1 (Ref)			
CCRT	2.79 (0.93–-8.31)	0.066		
CT	4.81 (1.5–14.96)	0.007		
RT	2.21 (0.71–6.86)	0.170		
Immediate complication				
No	1 (Ref)		1 (Ref)	
Yes	3.74 (1.60–8.76)	0.002	4.55 (1.35–15.27)	0.014
Late complication				
No	1 (Ref)		1 (Ref)	
Yes	2.61 (1.17–-5.83)	0.020	1.31 (0.31–5.48)	0.713
Radiation-induced colitis				
No	1 (Ref)			
Yes	1.49 (0.45–4.98)	0.519		
Radiation-induced cystitis				
No	1 (Ref)			
Yes	1.85 (0.69–4.95)	0.218		
> 12-mo ureter or urethra catheter use				
No	1 (Ref)			
Yes	2.93 (1.21–7.08)	0.017		
Recurrence				
No	1 (Ref)			
Yes	619.9 (7.9–48904)	0.004		
Recurrent site				
Nil	1 (Ref)			
Pelvis	623997 (0–2.453E65)	0.849		
Distant site	589728 (0–2.302E65)	0.849		
Both sites	1860001 (0–7.2E65)	0.837		

CCRT = concurrent chemoradiation; CT = chemotherapy; DSI = deep stromal invasion; LN = lymph node; LVSI = lymphovascular space invasion; NACT = neoadjuvant chemotherapy; R = radiation.

node positivity, subsequently resulting in a decrease in the risk factors that indicate adjuvant RT [15]. Reduction of tumor volume makes surgery easier (possibly less radical), especially parametrial resection, and thus, a reduction in the number of complications would be expected [26, 27]. In this study, NACT indeed significantly decreased the immediate complication rate, from 32% to 5.7%, although it did not statistically significantly decrease the need of postoperative adjuvant therapy (54.3% vs. 64%, $p = 0.452$), which also contributed to the absence of a significant difference in disease-free survival and OS between the NACT-RH and RH groups, respectively (99.7 ± 69.7 months vs. 90.0 ± 72.1 months, $p = 0.602$; 107.6 ± 60.4 months vs. 104.0 ± 60.2 months, $p = 0.821$, respectively). The reasons may be secondary to the study population, who were in a severe status, or the CT regimen itself [28]. For example, the rate of lymph node metastases was higher in the study population than in patients classified as conventional FIGO IB (32–37.1% vs. 10–18%). In addition, although tumor shrinkage was significant in the NACT–RH group (from 6.4 ± 0.5 cm to 4.5 ± 1.4 cm), the size of these tumors was still large (≥ 4 cm). That is why the worse outcome could be related to the bulky tumor size (≤ 5.3 cm. vs. > 5.3 cm with a HR of 10.66, $p < 0.001$) and the presence of para-aortic lymph node metastases (HR 8.33, $p = 0.010$).

However, we still highlight the value of NACT in those patients with marked bulky Cx-SCC who were scheduled to undergo RH, because NACT indeed made surgery easier, with less blood loss (558 ± 1328 mL vs. 930 ± 356 mL, $p < 0.001$) and a lower immediate complication rate in this study.

All patients who experienced recurrence died of the disease, suggesting that conventionally postoperative radiation-based adjuvant therapy might not be affective in the management of these patients after NACT-RH or RH treatment. Although those patients who were treated with postoperative adjuvant therapy significantly had more unfavorable pathological risk factors, especially presence of pelvic and/or para-aortic lymph node metastases (Table 2), the results of the current study were still consistent with those of our previous studies, showing any adjuvant therapy added little value for patients after RH or even though these patients had

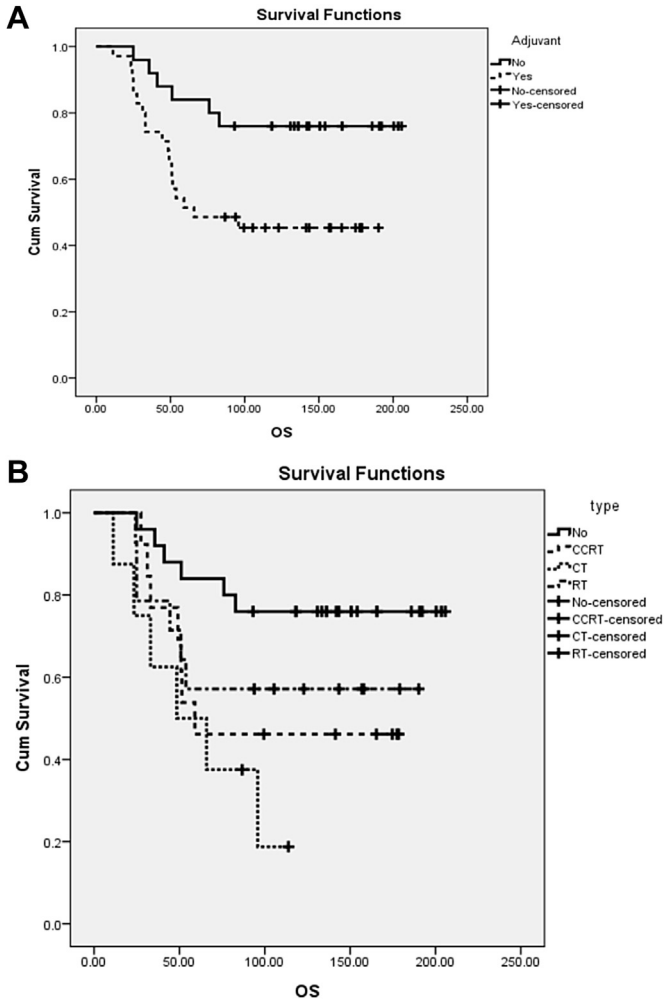

Fig. 3. The role of adjuvant therapy in patients with bulky squamous cell carcinoma of the cervix (≥ 6 cm) after primary treatment with either three courses of weekly cisplatin neoadjuvant therapy and radical hysterectomy or direct radical hysterectomy. (A) $p = 0.022$. (B) $p = 0.033$. OS = overall survival.

been treated with NACT, like patients with NACT-RH in the current study, if they were classified as a high-risk group based on the scoring system we proposed [1–22]. It was possible that the NACT regimen for these bulky-sized tumors needed a further investigation, because three courses of weekly cisplatin 50 mg/m^2 might not provide an adequate or significant tumor reduction and tumor size was still the most strongly and significantly risk factor for worse outcome of patients with bulky-sized Cx-SCC. It was also possible that conventionally postoperative radiation-based adjuvant therapy (CCRT or RT) might not be a better choice for those high-risk patients. Most of these patients (77%, 27/35) were treated with radiation-based adjuvant therapy (CCRT and RT) in the current study. By contrast, patients undergoing adjuvant therapy (who had worse pathologic risk factors) and patients without adjuvant therapy (who had less severe risk factors) had statistically similar survival in multivariate analysis, suggesting that adjuvant therapy might be beneficial to the patients in certain population who had worse pathologic risk factors, or chemotherapy could be considered as a postoperative adjuvant therapy, even though the role of chemotherapy is still uncertain for patients with Cx-SCC. Furthermore, a more active and intensive surgical approach might be needed, although the role of surgical removal of the positive lymph nodes for patients with Cx-SCC is still controversial. In the current study, the mean number of retrieved para-aortic lymph nodes was only three, and this might be relatively inadequate. A more extensive para-aortic lymphadenectomy to remove as many positive lymph nodes as possible might provide additional information to schedule more effective therapies (systemic treatment), including clinical trials, because every effort should be conducted to minimize a subsequent distant failure. By contrast, the question—is more radical more effective?—[26] was raised, because patients with a long-term ureter or urethra catheter use (more than 12 months after surgery) showed the worse prognosis. More trials are needed to determine how to balance the risks/benefits of treatment for these patients with highly risky and bulky-sized Cx-SCC to provide an opportunity of better survival.

There are some limitations in the current study. First, this was a retrospective study, and selection bias inherent to the type of design may have been introduced in this study. The best way to avoid or minimize this bias is to conduct a prospective randomized study, but there should be a high number of patients enrolled to show a statistically significant difference [2]. However, retrospective study with large datasets is still the best way to investigate this issue. Second, the sample size of patients was small in this study. But it is not easy to enroll an adequate number of patients with Cx cancer, especially with markedly bulky tumors, such as in ≥ 6-cm Cx-SCC, because Cx cancer may become a relatively rare disease in some areas in the future, if a nationwide screening program and the introduction of human papilloma virus vaccination in the teenage population can be continued. Third, the diagnoses of late complications were only made by the patients' needs for medical care, but the severity was not graded. In addition, late complications might not be totally revealed in the limited items, such as radiation colitis and cystitis, and long-term ureter or catheter use (≥12 months). Despite these limitations, this is a relatively large study with a long-term follow-up to investigate the potential role of NACT in the management of patients with Cx-SCC ≥ 6-cm.

Finally, without a randomized study comparing NACT-RH with CCRT [15] or the significant benefits of OS with a comparison of direct RH in this study, the choice of NACT-RH in the management of markedly bulky Cx-SCC, especially the use of three cycles of weekly 50 mg/m^2 cisplatin, would need further confirmation. However, we still believe that NACT is a feasible experimental treatment method, because in this study, we found a significant decrease in blood loss during operation, a decrease in the pathological tumor size and immediate complication rate.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

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